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(54) **PRESERVATIVE FREE BIMATOPROST AND TIMOLOL SOLUTIONS**

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(58) **Field of Classification Search**

None
See application file for complete search history.

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(57) **ABSTRACT**

The present invention is directed to preservative-free solutions of bimatoprost and timolol for lowering intraocular pressure and treatment of glaucoma.

8 Claims, No Drawings

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PRESERVATIVE FREE BIMATOPROST AND TIMOLOL SOLUTIONS

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/691,919, filed Apr. 21, 2015, which is a continuation of U.S. patent application Ser. No. 13/785,911, filed Mar. 5, 2013, now U.S. Pat. No. 9,061,034, issued Jun. 23, 2015, which is a continuation-in-part of U.S. patent application Ser. No. 13/812,597, filed May 30, 2013, now U.S. Pat. No. 9,078,854, issued Jul. 14, 2015, which is a national phase application under 35 U.S.C. § 371 of PCT Patent Application No. PCT/US11/45654, filed Jul. 28, 2011, which claims priority to Provisional Patent Application Ser. No. 61/368,685, filed Jul. 29, 2010, all of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

The present application is directed to preservative-free formulations of bimatoprost and timolol.

BACKGROUND OF THE INVENTION

Bimatoprost is a prostamide, a synthetic analog of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), with potent ocular hypotensive activity. Bimatoprost lowers intraocular pressure (IOP) in patients with glaucoma or ocular hypertension by increasing outflow of aqueous humor through both the trabecular meshwork and uveoscleral routes. Timolol is a non-selective beta-adrenergic receptor blocker and functions by reducing aqueous humor production through blockage of the beta receptors on ciliary epithelium.

Use of preservative containing eye drops has been implicated in the development or worsening of ocular surface disease. Management of open angle glaucoma and ocular hypertension require long term treatment with eye drops containing preservatives. Symptoms and signs of ocular surface disease such as ocular surface breakdown, irritation, burning, foreign body sensation, dryness, inadequate quantity of tears, etc. are prevalent in a large proportion of patients with open angle glaucoma and ocular hypertension.

Compared to eye drops preserved with benzalkonium chloride, preservative-free eye drops induce significantly fewer ocular symptoms and signs of irritation in patients, such as pain or discomfort, foreign body sensation, stinging or burning, and dry eye sensation.

Patients experiencing hypersensitivity reactions with benzalkonium chloride cannot use a commercial bimatoprost product containing benzalkonium chloride which is preserved even with 0.005% w/v benzalkonium chloride. Benzalkonium chloride also may be absorbed by the soft contact lenses therefore patients wearing soft contact lenses are advised to remove lenses prior to administration and wait at least 15 minutes before reinserting them.

SUMMARY OF THE INVENTION

The present invention is directed to a bimatoprost and timolol solutions without benzalkonium chloride or any

other preservative which will be superior from a safety and tolerability standpoint while at least maintaining and/or improving its efficacy of IOP lowering and be available for use by patients hypersensitive to benzalkonium chloride and be convenient for patients wearing soft contact lenses.

Bimatoprost and timolol ophthalmic solution without preservative is a clear to slightly yellow, isotonic, sterile solution. The drug product contains bimatoprost and timolol as the active ingredients. The inactive ingredients are tonicity and buffer agents, and purified water. Suitable buffers such as sodium phosphate dibasic heptahydrate and citric acid monohydrate and suitable tonicity agents such as sodium chloride may be included. The solution is an aqueous solution having a pH value within the range of about 7 to about 8, and preferably about 7.3. Suitable buffers may be included, such as sodium phosphate dibasic heptahydrate, citric acid monohydrate. Preferably, the tonicity agent such as sodium chloride will be employed in an amount to provide a final osmotic value of at least about 200 mOsm/kg, preferably from about 280 to about 370 mOsm/kg.

The present invention can be made generally according to the teachings of U.S. patent application Ser. No. 10/153,043 which is hereby incorporated by reference in its entirety.

Some embodiments of the invention include the following:

- 1) A preservative free bimatoprost and timolol composition for lowering intraocular pressure in a human patient comprising the following formulation: about 0.03% w/v bimatoprost; about 0.5% timolol and having no preservative.
- 2) The preservative free bimatoprost and timolol solution of paragraph 1 for lowering intraocular pressure in a human patient comprising the following formulation: 0.03% w/v bimatoprost; 0.5% timolol; 0.268% w/v Sodium Phosphate Dibasic Heptahydrate; 0.014% Citric Acid Monohydrate; about 0.68% sodium chloride, hydrochloric acid, water, sodium hydroxide and having a pH of about 7.3.
- 3) The preservative free bimatoprost and timolol solution of paragraphs 1 and 2, wherein the timolol is timolol maleate at 0.68% w/v.
- 4) A composition as described in Table 1.
- 5) The bimatoprost and timolol solution of paragraphs 1-4, wherein the solution is useful for treating glaucoma.
- 6) The bimatoprost and timolol composition of paragraphs 1-4, wherein the composition is a solution wherein the solution is contained in a unit dose kit form.
- 7) The bimatoprost and timolol composition of any of paragraphs 1-6, wherein the composition is applied once a day to each eye.
- 8) The bimatoprost and timolol composition of any of paragraphs 1-6, wherein the composition is applied twice a day to each eye.
- 9) The bimatoprost and timolol compositions of paragraphs 1-4, wherein the composition has greater bioavailability of bimatoprost and timolol in the eye of the patient with fewer side-effects than bimatoprost and timolol preserved with benzalkonium chloride or another preservative.
- 10) The composition of paragraph 1, wherein the composition may be a solution, emulsion, dispersion, suspension, reverse emulsion and microemulsion.
- 11) The composition of paragraph 1, wherein the composition is contained in a unit-dose vial.

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12) The composition of paragraph 1, wherein the composition is contained in a multi-dose vial which has anti-preservative properties such as metal-ions imbedded in its dispensing tip.

13) The composition of paragraph 12, wherein the metal ions are silver ions.

14) The bimatoprost and timolol composition of paragraph 1, wherein the composition has better intraocular lowering ability and fewer side-effects than the same composition preserved with benzalkonium chloride.

DETAILED DESCRIPTION OF THE INVENTION

A bimatoprost and timolol ophthalmic formulation of the present invention without preservative is shown in Table 1.

TABLE 1

| Example of bimatoprost and timolol ophthalmic solution without preservative according to the present invention: | | | |
|---|-------|---------------|--------|
| Ingredients | Units | Grade | Amount |
| Bimatoprost | % w/v | N/A | 0.03 |
| Timolol Maleate | % w/v | USP/Ph Eur | 0.68 |
| Sodium Phosphate Dibasic Heptahydrate | % w/v | USP | 0.268 |
| Citric Acid Monohydrate | % w/v | USP/Ph Eur | 0.014 |
| Sodium Chloride | % w/v | USP/Ph Eur | 0.68 |
| Hydrochloric Acid | % w/v | USP/Ph Eur | pH 7.3 |
| Sodium Hydroxide | % w/v | USP/Ph Eur | pH 7.3 |
| Purified Water/WFI | Q.S. | USP/Ph Eur | QS |

The present invention is directed to formulations of bimatoprost and timolol without benzalkonium chloride as a preservative and may be marketed in unit dose form. As a result of the removal of benzalkonium chloride, the present invention results in the same as or greater bioavailability of the active ingredients bimatoprost and timolol in the eye without the unwanted side-effects associated with the preservative benzalkonium chloride such as hyperemia, which will improve efficacy of the product in lowering IOP per dosage unit, with superior patient compliance and fewer side-effects. Other side effects which may be avoided with the preservative free compositions of the present invention include, blepharitis, corneal erosion, depression, epiphora, eye discharge, eye dryness, eye irritation, eye pain, hyperemia, allergic conjunctivitis, eyelid edema, eyelid erythema, eyelid pruritus, foreign body sensation, headache, hypertension, oral dryness, somnolence, superficial punctate keratitis, and visual disturbance.

Example 1

Ganfort® is a fixed combination of bimatoprost 0.03%/timolol 0.5% with 50 ppm benzalkonium chloride (BAK, as preservative) used in a number of countries worldwide as an effective treatment for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular

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hypertension (OHT). A preservative-free (PF) formulation of Ganfort®, hereafter referred to as Ganfort® PF, has been developed to cater to diverse patients needs. Ganfort® PF is the same formulation as that of Ganfort®, except for the removal of 50 ppm BAK. The use of a preservative-free formulation is preferred for patients who have a known sensitivity to preservatives or where preservative use is a concern particularly in patients with dry eyes or other ocular surface disorders.

The IOP lowering efficacy of a PF formulation of the bimatoprost component of Ganfort® was studied: In a 5-day, 30 patient, randomized, masked, paired-eye comparison study of bimatoprost 0.03 PF with bimatoprost 0.03% (preserved with 50 ppm BAK), the treatment difference (i.e. bimatoprost PF minus bimatoprost preserved) in IOP lowering efficacy on Day 5 ranged from +0.07 mmHg to +0.53 mmHg, favoring the preserved formulation (Clinical Study Report on file); In a 12 week, 597 patient, multi-center, randomized, masked, parallel group study, the a-priori defined primary efficacy analysis of IOP change from baseline in worse eye IOP at week 12 (per protocol population), showed a treatment difference of +0.02 to +0.32 mmHg favoring bimatoprost preserved (Clinical Study Report on file). Based on the results of these studies, and the known penetration enhancing effects of BAK, it was anticipated that the removal of BAK from Ganfort® PF would result in a reduction in its IOP lowering effect, though this may not be statistically significant.

For development of Ganfort® PF, a 12 week, multi-center, randomized, masked study was conducted in 561 patients with glaucoma or ocular hypertension, comparing the efficacy and safety of Ganfort® PF with Ganfort®. IOP was measured at 3 time points (hour 0, hour 2 and hour 8), at each of the study visits (baseline, weeks 2, 6 and 12). The study was designed to test for statistical non-inferiority as well as statistical equivalence of PF formulation with preserved formulation, based on pre-established criteria using IOP margins of 1.5 mmHg Differences in the IOP lowering effects of the two formulations (Ganfort® PF minus Ganfort®) were evaluated, where a negative difference is indicative of greater IOP lowering by Ganfort® PF.

At baseline, no statistically or clinically significant differences in worse eye IOP (identified as the eye with higher baseline IOP) or average eye IOP (average IOP of both eyes) were observed between the Ganfort® PF and Ganfort® groups. While Ganfort® PF met the criteria for statistical non-inferiority and equivalence with Ganfort® based on the a priori established statistical criteria, the differences in treatments (Ganfort® PF-Ganfort®) in IOP lowering from baseline at all of the 9 follow-up time points (hours 0, 2 and 8, at weeks 2, 6 and 12), favored Ganfort® PF:

1) In a-priori defined primary analysis at week 12 (per protocol population), the treatment difference in change from baseline in worse eye IOP was -0.30 to -0.37 mmHg;

2) Across the 12 week study (ITT population), the treatment difference in change from baseline for worse eye IOP ranged from -0.12 to -0.54 mmHg, favoring Ganfort® PF at all follow up time points; and,

3) The treatment difference in change from baseline for average eye IOP ranged from -0.19 to -0.49 mmHg during weeks 2 to 12, favoring Ganfort® PF at all follow up time points.

TABLE I

| Baseline and Change From Baseline in IOP (mm Hg) in Study of Example I | | | | | | | | |
|--|------|-----------|---------------------------------|------------------------|-------------------------------------|----------------------------------|------------------------|-------------------------------------|
| Visit | Hour | Statistic | Worse Eye IOP ^a (PP) | | | Worse Eye IOP ^a (ITT) | | |
| | | | GANFORT ® PF (N = 256) | GANFORT ® (N = 260) | Difference (95% CI) ^c | GANFORT ® PF (N = 278) | GANFORT ® (N = 283) | Difference (95% CI) ^d |
| | | | Baseline | 0 | Mean | 25.41 | 25.38 | 0.01 |
| | | SD | 2.232 | 2.209 | (-0.35, 0.37) | 2.233 | 2.244 | (-0.27, 0.42) |
| | 2 | Mean | 24.79 | 24.72 | 0.04 | 24.71 | 24.61 | 0.14 |
| | | SD | 2.676 | 2.470 | (-0.38, 0.47) | 2.700 | 2.536 | (-0.27, 0.54) |
| | 8 | Mean | 23.88 | 23.82 | 0.06 | 23.81 | 23.80 | 0.06 |
| | | SD | 3.008 | 2.747 | (-0.39, 0.50) | 2.989 | 2.795 | (-0.36, 0.49) |
| Week 2 | 0 | Mean | -9.16 | -8.94 | -0.27 | -9.01 | -8.65 | -0.36 |
| | | SD | 3.280 | 3.162 | (-0.75, 0.21) | 3.245 | 3.327 | (-0.81, 0.09) |
| | 2 | Mean | -8.66 | -8.46 | -0.26 | -8.53 | -8.17 | -0.37 |
| | | SD | 3.593 | 3.188 | (-0.73, 0.20) | 3.688 | 3.368 | (-0.82, 0.07) |
| | 8 | Mean | -8.45 | -8.14 | -0.29 | -8.22 | -7.85 | -0.43 |
| | | SD | 3.377 | 3.062 | (-0.73, 0.16) | 3.507 | 3.290 | (-0.85, 0.00) |
| Week 6 | 0 | Mean | -8.93 | -9.03 | -0.01 | -8.89 | -8.79 | -0.12 |
| | | SD | 3.170 | 3.148 | (-0.47, 0.45) | 3.246 | 3.312 | (-0.57, 0.33) |
| | 2 | Mean | -8.71 | -8.60 | -0.38 | -8.69 | -8.22 | -0.54 |
| | | SD | 3.601 | 3.442 | (-0.84, 0.08) | 3.695 | 3.619 | (-0.98, -0.09) |
| | 8 | Mean | -7.99 | -8.05 | -0.09 | -7.94 | -7.80 | -0.23 |
| | | SD | 3.412 | 3.272 | (-0.54, 0.37) | 3.454 | 3.473 | (-0.67, 0.21) |
| Week 12 | 0 | Mean | -9.06 | -8.72 | -0.37 | -8.94 | -8.51 | -0.46 |
| | | SD | 3.216 | 3.088 | (-0.83, 0.10) | 3.290 | 3.253 | (-0.91, -0.01) |
| | 2 | Mean | -8.53 | -8.38 | -0.30 | -8.44 | -8.08 | -0.40 |
| | | SD | 3.520 | 3.297 | (-0.73, 0.14) | 3.646 | 3.504 | (-0.83, 0.03) |
| | 8 | Mean | -7.98 | -7.72 | -0.36 | -7.87 | -7.52 | -0.45 |
| | | SD | 3.435 | 3.172 | (-0.78, 0.07) | 3.496 | 3.362 | (-0.86, -0.03) |

| Average Eye IOP ^b (ITT) | | | | | | |
|------------------------------------|------|-----------|-----------------|------------------------|-------------------------------------|--|
| Visit | Hour | Statistic | GANFORT ® | | Difference (95% CI) ^e | |
| | | | PF (N = 278) | GANFORT ® (N = 283) | | |
| Baseline | 0 | Mean | 24.94 | 24.86 | 0.11 | |
| | | SD | 2.116 | 2.131 | (-0.21, 0.43) | |
| | 2 | Mean | 24.29 | 24.23 | 0.09 | |
| | | SD | 2.515 | 2.426 | (-0.29, 0.46) | |
| | 8 | Mean | 23.42 | 23.36 | 0.10 | |
| SD | | 2.904 | 2.703 | (-0.30, 0.51) | | |
| Week 2 | 0 | Mean | -8.72 | -8.37 | -0.40 | |
| | | SD | 3.065 | 3.196 | (-0.88, 0.08) | |
| | 2 | Mean | -8.24 | -8.00 | -0.33 | |
| | | SD | 3.466 | 3.232 | (-0.82, 0.16) | |
| | 8 | Mean | -7.94 | -7.53 | -0.49 | |
| SD | | 3.368 | 3.203 | (-0.97, -0.01) | | |
| Week 6 | 0 | Mean | -8.66 | -8.55 | -0.19 | |
| | | SD | 3.052 | 3.153 | (-0.67, 0.29) | |
| | 2 | Mean | -8.39 | -8.05 | -0.48 | |
| | | SD | 3.467 | 3.424 | (-0.97, 0.02) | |
| | 8 | Mean | -7.71 | -7.54 | -0.26 | |
| SD | | 3.324 | 3.340 | (-0.75, 0.22) | | |
| Week 12 | 0 | Mean | -8.65 | -8.30 | -0.45 | |
| | | SD | 3.109 | 3.009 | (-0.92, 0.02) | |
| | 2 | Mean | -8.11 | -7.86 | -0.38 | |
| | | SD | 3.392 | 3.413 | (-0.87, 0.11) | |
| | 8 | Mean | -7.57 | -7.27 | -0.43 | |
| SD | | 3.395 | 3.226 | (-0.92, 0.05) | | |

GANFORT ® PF = bimatoprost 0.3 mg/mL + timolol 5 mg/mL preservative-free;

IOP = intraocular pressure;

ITT = intent-to-treat;

PP = per protocol

In the ITT population, missing values were imputed using the last observation carried forward (LOCF) method.

^aWorse eye refers to the eye with the worse baseline IOP, which was determined as the eye with the higher mean diurnal IOP at baseline. If both eyes had the same mean diurnal IOP at baseline, the right eye was designated as the worse eye.

^bAverage eye IOP refers to the average IOP of both eyes.

^cConfidence intervals (CI) are based on the analysis of covariance (ANCOVA) model with treatment and investigator as main effects and baseline worse eye IOP as the covariate. Estimated difference (bimatoprost 0.3 mg/mL + timolol 5 mg/mL PF minus GANFORT ®) is based on the least-squares means from the ANCOVA model. If patients had baseline IOP value excluded due to protocol deviations then they were not included in the change from baseline analyses.

^dCI's are based on the ANCOVA model with treatment and investigator as main effects and baseline worse eye IOP as the covariate. Estimated difference (bimatoprost 0.3 mg/mL + timolol 5 mg/mL PF minus GANFORT ®) is based on the least-squares means from the ANCOVA model.

^eCI's are based on the analysis of variance (ANOVA) model with treatment and investigator as fixed effects. Estimated difference (bimatoprost 0.3 mg/mL + timolol 5 mg/mL PF minus GANFORT ®) is based on the least-squares means from the ANOVA model. Source: Clinical Study Report on file

Other analysis of efficacy produced similar results. Hence Ganfort® PF, showed consistently numerically greater IOP reduction than Ganfort®.

Treatment in patients with glaucoma or OHT is aimed at lowering IOP in order to preserve visual function and hence quality of life. The impact of IOP reduction on disease progression have been well established (Kass et al, 2002; AGIS, 2000; Heijl et al, 2002), with data indicating that for each 1 mmHg of IOP reduction, the risk of progression is reduced by approximately 10% (Litchter, 2002; Leske et al, 2007). Preservative free formulations offer an alternative treatment for patients who are sensitive to preservatives or who have susceptibility to preservative-related ocular surface adverse events. However, with the known penetration enhancing effects of BAK, it is anticipated that a loss in efficacy will be seen, in which case the treating physician has to balance treatment tolerability for a particular patient versus the undesired loss of IOP lowering efficacy. The results of the above-described study, showing an increased IOP lowering effect of removal of BAK in the Ganfort® PF formulation is an unexpected finding that can benefit patients with glaucoma and OHT who often require efficacious, long term treatment.

BAK Effect

Given the known penetration enhancing effect of benzalkonium chloride (BAK), which is a preservative used in many marketed ophthalmic products, it was expected that Ganfort® Preservative Free (PF), which does not contain the 50 ppm BAK present in Ganfort®, would result in lower ocular bioavailability of both bimatoprost and timolol, and consequently be less effective in lowering IOP than Gan-

fort®. Therefore, data from the above described study contradicted conventional wisdom.

What is claimed is:

1. A preservative free bimatoprost and timolol composition for lowering intraocular pressure in a patient comprising the following formulation: about 0.03% w/v bimatoprost and about -0.68% w/v timolol maleate and having no preservative.

2. The preservative free bimatoprost and timolol composition of claim 1 for lowering intraocular pressure in a patient comprising the following formulation: 0.03% w/v bimatoprost; -0.68% w/v timolol maleate 0.268% w/v Sodium Phosphate Dibasic Heptahydrate; 0.014% w/v Citric Acid Monohydrate; about 0.68% w/v sodium chloride; water and having a pH of about 7.3.

3. The bimatoprost and timolol composition of claim 1, wherein the composition is a solution and is useful for treating glaucoma.

4. The bimatoprost and timolol composition of claim 1, wherein the composition is contained in a unit dose kit form.

5. The bimatoprost and timolol composition of claim 1, wherein the composition is applied once a day to each eye.

6. The bimatoprost and timolol composition of claim 1, wherein the composition is applied twice a day to each eye.

7. The bimatoprost and timolol composition of claim 1, wherein the composition has better intraocular lowering ability and fewer side-effects than the same composition preserved with benzalkonium chloride.

8. The bimatoprost and timolol composition of claim 1, wherein the composition is a solution contained in a unit dose vial.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,058,560 B2
APPLICATION NO. : 15/677665
DATED : August 28, 2018
INVENTOR(S) : Sukhon Likitlersuang et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title Page

On the page 2, in item (56), in Column 1, under "Other Publications", Line 2, delete "Row," and insert -- Flow, --, therefor.

On the page 2, in item (56), in Column 1, under "Other Publications", Line 48, delete "Bimatoprost" and insert -- Bimatoprost --, therefor.

On the page 2, in item (56), in Column 2, under "Other Publications", Line 21, delete "Junich," and insert -- Junichi, --, therefor.

On the page 2, in item (56), in Column 2, under "Other Publications", Line 47, delete "2003," and insert -- 2008, --, therefor.

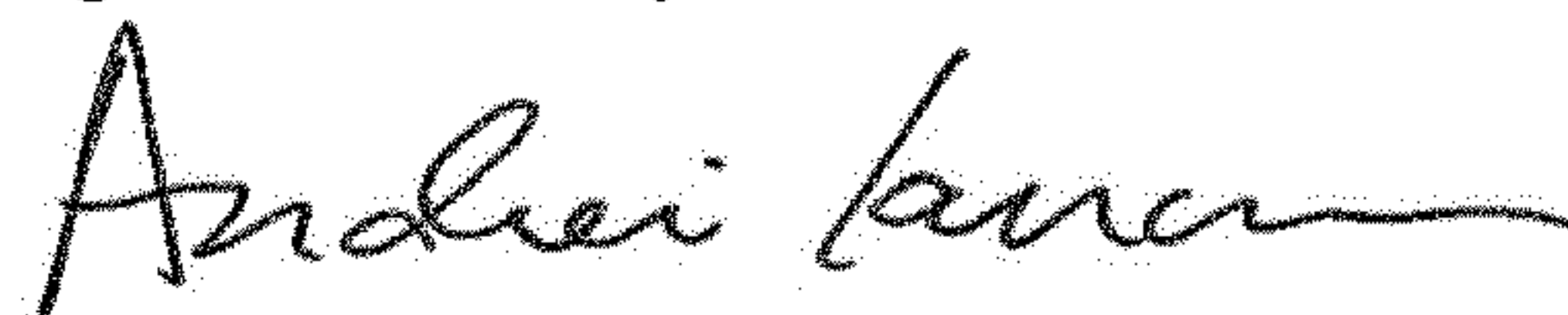
On the page 3, in item (56), in Column 1, under "Other Publications", Line 7, delete "63." and insert -- 68. --, therefor.

In the Claims

In Column 8, Line 7, in Claim 1, delete "-0.68%" and insert -- 0.68% --, therefor.

In Column 8, Line 12, in Claim 2, delete "-0.68% w/v timolol maleate" and insert -- 0.68% w/v timolol maleate; --, therefor.

Signed and Sealed this
Eighteenth Day of December, 2018



Andrei Iancu
Director of the United States Patent and Trademark Office